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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/260,468	03/02/1999	JAMES ROBL	000270 - 057	6587

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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	20

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/260,468	ROBL ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-19,21-30 and 32-61* is/are pending in the application.

4a) Of the above claim(s) *26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-19,21-25 and 32-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on May 20, 2002, paper number 19, has been entered.

DETAILED ACTION

This application filed March 2, 1999, is a continuation in part of 09/032.945, filed March 2, 1998, now abandoned, which is a continuation in part of 08/699,040, filed August 19, 1996, now abandoned.

As indicated in the request for continued examination, the after final amendment filed November 21, 2001 (replacement copy filed with supporting evidence on April 24, 2002), paper number 15, has been entered. Claim 1 has been amended. Claims 58-61 have been added. Claims 1, 2, 4-19, 21-30, 32-61 are pending. Claims 26-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 8.

Claims 1, 2, 4-19, 21-25 and 32-61 are currently under examination.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claim 19 be found allowable, claims 21-23 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case, each of the claims encompass the product as it is drawn to a human embryonic stem-like cell. It is recognized that each of the claims indicate the cell is obtained by different methods, however the methods do not materially alter the end product being claimed. Additionally, upon review of the instant specification Examiner can only find general description of attributes of an embryonic stem readily recognized in the art and can not find support for how

the various methods would result in a human embryonic stem cell that is different or that such differences are contemplated. Therefore, because each claim recites and encompasses a human embryonic stem cell they are each equivalent to one another.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-19, 21-25, 32-52 and 58-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the claim embodiment that the mitochondrial DNA be from a species other than that of the nuclear material is considered new matter. Upon review of the specification, the only support for the mtDNA and nuclear DNA in the embryonic stem cells being from different species is a general discussion that 'stem-like cells ***may*** possess the mitochondria of the oocytes' (***emphasis added*** page 14, lines 4-5). Beyond this general teaching that a resulting cell may possess this characteristic, the specification fails to provide any specific guidance on how to actively make such a cell, or how to specifically identify this cell type.

Further, the methods as instantly claimed do not comprise an active step wherein such a cell is obtained, only that the cell is isolated from a cultured NT unit (see claim 1 for example). Though a NT unit comprising mtDNA from the oocyte and nuclear material from a different species ***may*** be generated practicing the method as claimed, this appears to be at most recognized as a consequence of practicing methods known in the art, not specifically contemplated as Applicants' invention.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 1, 2, 4-19, 21-25, 32-52 and 58-60 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

Claims 1, 2, 4-19, 21-25, 32-52 and 58-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Three issues are the focus for the basis for the enablement rejection: first, the ability to selectively generate viable nuclear transfer unit (NT) embryos with nuclear material and mitochondrial from two different species; second, the ability to successfully culture such a NT unit beyond a given cell number; and third, the ability to isolate or derive embryonic stem like cells from such a cultured NT unit. It is noted that dependent claims are drawn to and encompass the cells generated by this method and uses of these cells in therapeutic methods which each have specific points of lack of enablement recognized in the art that are not remedied by the instant specification. However, a detailed discussion of these claims will not be addressed because of the failure of the specification to enable the methodology to use transpecies nuclear transfer to generate embryonic stem cells.

Initially, Examiner notes that the instant specification general provides support for the embodiment in the preamble that the resulting NT unit **may** have nuclear material from one species and the mitochondria from the oocyte of a different species (see page 14, lines 1-6). Presently, the art of nuclear transfer as exemplified in the use of generating cloned animals, most notably in the cloning of the sheep Dolly, clearly supports that the mitochondria from the recipient oocyte may become the dominant form of mtDNA in the resulting animal. However, neither the specification nor the art specifically teach how to specifically or actively obtain a NT

unit or cells cultured therefrom. Importantly, the specification while recognizing that this '***may*** possess the mitochondria of the oocytes used for nuclear transfer' (***emphasis added***, page 14, lines 4-5) and may be a characteristic of a resulting NT cell it does not teach that it will necessarily be a characteristic. Further, the specification fails to provide the specific methodology of obtaining or forcing the resulting NT cell to have mt DNA heterologous to the nuclear material, or even the methods of identifying such a cell. In addition, immediately proceeding the teaching for the potential of having mtDNA from the oocyte the specification hypothesizes on the factors present in the oocyte which are necessary or required for further maturation of the resulting NT unit, however the relevance or importance of mtDNA in this process is not addressed. Finally, it is noted that the specification does not provide any new or novel methodology as it is drawn to practicing nuclear transfer techniques and relies on the detailed teaching in the art to practice the instantly claimed method (see for example citations of known methods on page 16, lines 13-21). Again, as noted above regarding the specification, upon review of these cited references, none of the teachings in the art specifically teach methodology to include or exclude mtDNA from the resulting NT unit. In general, Examiner would agree that the methodology of nuclear transfer as taught in the specification may result in a cell in which the mtDNA from the oocyte becomes the dominant form of mtDNA in cultured cells as evidenced in the art analyzing cloned animals made by nuclear transfer. However, more to the point of the enablement rejection is the ability of mtDNA to complement the nuclear material from a different species. As summarized by the instant specification at the time of filing

the methodology for nuclear transfer was known and practiced for use in generating cloned animals and in the study of embryological development. Further, at the time of the claimed invention, methods of nuclear transfer wherein the nuclear material and the recipient oocyte where from different species was already performed. For example, Wolfe *et al.* (Theriogenology, 33(1):350, 1990) teach that the affects of intergeneric nuclear transplantation was studied and that species more distant from the cow were less capable of supporting growth and deafferentation of the resulting NT unit. Even more broadly reviewed, Gurdon (J. Cell Sci 4:287-318, 1986) teaches that species as distant as human and Xenopus have been tested by nuclear transfer, and while capable of supporting several cell divisions, is always lethal usually arresting at an irregular blastulae (page 300). While Wolfe *et al.* and Gurdon do not specifically teach what causes the arrest in development, Meirelles *et al.* (Genetics 158:351-356) teach that while mitochondrial heteroplasmy may occur in systems with related nuclear and mitochondrial DNA, even unrelated species of Bovus do not support the full development of a nuclear transfer unit generated by more distant species. A more recent review by Dominko *et al.* (Biol of Reprod 60:1496-1502, 1999) provides a even more generally review for the use of distant mammalian species clearly teaching the necessity of testing the compatibilities of cytoplasmic (i.e. mtDNA) and nuclear DNA when practicing interspace NT (see summary on page 1501). Therefore, based on the art of record only species with closely related nuclear and cytoplasmic genes would be capable of successfully reconstituting the genetic complement necessary for development of an embryo (see summary in abstract). Additionally, while not specifically encompassed by the

instant claims, it should also be noted that at the time of filing and currently nuclear transfer using an oocyte and differentiated cell from the same species while attempted has not been successfully carried out for a wide variety of mammalian species, clearly suggesting that even within a species the methodology of nuclear transfer and the ability of an oocyte to support embryonic development of any differentiated cell still can not successfully be obtained. The simple reliance of the instant specification on nuclear transfer methodology known in the art fails to address even such limitations of successfully practicing intraspecies nuclear transfer (see for example Aronson *et al.* (Current Topics in Devolopmental Biology 23: 55-71). Moreover, the art teaches that embryonic stem cells from the broad range of animals encompassed by the instant claims encompassed by the claims have not been successfully isolated from normal embryos. The present specification provides no further guidance providing the necessary methodology required to isolate embryonic stem cells beyond those readily known in the art. In summary, while the methods of inserting the nuclear material from one species into the oocyte of another different species was known and practiced at the time of the claimed invention, the methodology to successfully culture the resulting NT unit into a blastocyst from which ES cells could be obtained was not successfully practiced. The instant specification relies in great part on the teaching in the art to practice nuclear transfer methodology and fails to address art recognized shortcomings for successfully culturing transpecies NT unit cells from distantly related species. Further, lacking the ability to obtain a viable NT unit capable of forming a viable embryo containing embryonic stem cells, the specification fails to provide the necessary guidance to

isolate and culture embryonic stem cells from species from which embryonic stem cells have not been derived.

With respect to the working examples provided in the present specification for cell culture obtained from introducing human nuclear material into a cow embryo, as indicated in the previous office action the morphological characterization of the resulting cells is insufficient to establish that the cells are in fact embryonic stem cells. Consistent with this view subsequent peered reviewed articles have questioned the lack of substantive data support for the instant claims (Science 282:1390-1391, 1998). Moreover, even if the cells represent human embryonic stem like cells, there is no evidence that the resulting cells characterized in the specification have mitochondria from the cow and thus fairly support enablement of the method claims or the resulting 'human' embryonic stem like cells.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,

except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English.

Claims 53, 54 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Gurdon (J. Cell. Sci., 1986).

Gurdon summarizes the early success of nuclear transfer in mammals (page 312, citing the work of Hoppe, Illmensee, Kelly and McGrath). Further, in the description of nuclear transfer between species, the experiments proposed are general and focus on the analysis of affects on development of maternal factors and chromosomal factors (pages 301-302). With respect to claim 53, it is noted the nuclear material is obtained from a mammalian species, and that the particular example of a mammal nucleus fused to a xenopus oocyte would anticipate this claim and the product set forth in claim 57. Further, while such a xenopus/mammalian NT unit is incapable of being cultured for an extended number of cell divisions or forming an intact embryo, the working example does meet the limitation set forth in claim 54.

Accordingly, Gurdun clearly anticipates claims 53, 54 and 57.

Claims 53-57 and 61 are rejected under 35 U.S.C. 102(e) as being anticipated by Stice *et al.* (WO 95/17500).

Stice *et al.* teach nuclear transfer procedures for producing non-human chimeric animals. Specifically, nuclear transfer techniques are used to introduce the nuclear material of one species

of animal into the enucleated oocyte of a recipient animal (entire disclosure and specifically claimed in claims 1-39). Stice *et al.* teach that various combinations of species can be done and provide working examples where the oocyte is cultured for 16 hours, enucleated and donor nuclear material is transferred to the perivitelline space and fused by electrofusion (pages 35-44).

Accordingly, Stice *et al.* anticipates claims 53-57 and 61.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 53-57 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Prather *et al.* (Biology of Reproduction, 1987, IDS reference), Gurdon (J. Cell. Sci. , 1986), Campbell *et al.* (WO 97/07668, March 1997, IDS reference), Telford *et al.* (Molecular

Reproduction and Development, 1990, IDS reference), Dominko *et al.* (Molecular Reproduction and Development, 1997, IDS reference) in further view of Stice *et al.* (WO 95/17500).

Campbell *et al.* provides a recent status of nuclear transfer techniques, and in particular, Campbell teaches the use of donor cells which have been arrested in Go by various methods, maturation curves of the bovine oocyte, and activation of the NT unit by various techniques known in the art. Further, Campbell teaches that the described nuclear transfer technology can be used to generate transgenic animals as well (entire reference; summarized in abstract and specifically claimed). Additionally, Dominko *et al.* and Telford *et al.* both provide further guidance for the optimization of in using bovine oocyte. Specifically, Dominko *et al.* demonstrate that there is an increased efficiency in embryo development when the genetic material is transferred later that 8 hours of culturing (Figures 3 and 4). Further, Stice et al. teaches that embryos that activation for most domestic animals will range from 16-52 hours (page 23; lines 16-27). In view of the work of Stice *et al.* and Dominko *et al.* it is clear that to establish the control of the genetic material transferred by nuclear transfer techniques, at least in the bovine, the artisan would deliver the nuclei after different culture transition periods.

Therefore, in view of the art as a whole, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to generate chimeric embryos by nuclear transfer techniques. As noted in Gurdon and Stice *et al.*, cross-species nuclear transfer has been performed for prior to the time of the claimed invention, however it was also observed that optimization of the methods wold be necessary. Campbell *et al.*, Telford *et al.*

and Dominko *et al.* provide such optimization conditions detailing specific method steps and materials necessary to increase embryo development for the cow. One of skill in the art would have been motivated to use the teachings of Campbell *et al.*, Telford *et al.* and Dominko *et al.* because at the time of the claimed invention they represented the latest and best conditions/methods available to practice nuclear transfer techniques.

Thus, the claimed invention, as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed. Claims 1, 2, 4-19, 21-25, 32-52 and 58-60 are free of the art of record, however they are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach

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